

FILE 'MEDLINE'  
FILE 'JAPIO'  
FILE 'BIOSIS'  
FILE 'SCISEARCH'  
FILE 'WPIDS'  
FILE 'CAPLUS'  
FILE 'EMBASE'

=> s grf4  
6 FILES SEARCHED...  
L1 7 GRF4

=> s l1 and (ras or rap1)  
L2 2 L1 AND (RAS OR RAP1)

=> dup rem l1  
PROCESSING COMPLETED FOR L1  
L3 3 DUP REM L1 (4 DUPLICATES REMOVED)

=> d l3 ibib abs 1-3

L3 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 2001:492702 BIOSIS  
DOCUMENT NUMBER: PREV200100492702  
TITLE: Data mining the Arabidopsis genome reveals fifteen 14-3-3 genes. Expression is demonstrated for two out of five novel genes.  
AUTHOR(S): Rosenquist, Magnus (1); Alsterfjord, Magnus; Larsson, Christer; Sommarin, Marianne  
CORPORATE SOURCE: (1) Department of Plant Biochemistry, Lund University, SE-221 00, Lund: magnus.rosenquist@plantbio.lu.se Sweden  
SOURCE: Plant Physiology (Rockville), (September, 2001) vol. 127, No. 1, pp. 142-149. print.  
ISSN: 0032-0889.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB In plants, 14-3-3 proteins are key regulators of primary metabolism and membrane transport. Although the current dogma states that 14-3-3 isoforms are not very specific with regard to target proteins, recent data suggest that the specificity may be high. Therefore, identification and characterization of all 14-3-3 (GF14) isoforms in the model plant Arabidopsis are important. Using the information now available from The Arabidopsis Information Resource, we found three new GF14 genes. The potential expression of these three genes, and of two additional novel GF14 genes (Rosenquist et al., 2000), in leaves, roots, and flowers was examined using reverse transcriptase-polymerase chain reaction and cDNA library polymerase chain reaction screening. Under normal growth conditions, two of these genes were found to be transcribed. These genes were named grf11 and grf12, and the corresponding new-14-3-3 isoforms were named GF14omicron and GF14iota, respectively. The gene coding for GF14omicron was expressed in leaves, roots, and flowers, whereas the gene coding for GF14iota was only expressed in flowers. Gene structures and relationships between all members of the GF14 gene family were deduced from data available through The Arabidopsis Information Resource. The data clearly support the theory that two 14-3-3 genes were present when eudicotyledons diverged from monocotyledons. In total, there are 15 14-3-3 genes (grfs 1-15) in Arabidopsis, of which 12 (grfs 1-12) now have been shown to be expressed.

L3 ANSWER 2 OF 3 WPIDS (C) 2003 THOMSON DERWENT DUPLICATE 1  
ACCESSION NUMBER: 2000-499228 [44] WPIDS  
DOC. NO. NON-CPI: N2000-370021  
DOC. NO. CPI: C2000-149852  
TITLE: Nucleic acids encoding guanine nucleotide releasing factor-4 useful for the treatment of cancers and neuronal disorders.  
DERWENT CLASS: B04 D16 S03  
INVENTOR(S): PHAM, N; ROTIN, D  
PATENT ASSIGNEE(S): (HSCR-N) HSC RES & DEV LP; (PHAM-I) PHAM N; (ROTI-I) ROTIN D  
COUNTRY COUNT: 90  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
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WO 2000043510 A2 20000727 (200044)\* EN 88  
 RW: AT BE CH CY DE DK EA FI FR GB GH GM GR IE IT KE LS MC MW NL  
 OA PT SD SE SL SZ T2 ZW  
 W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES  
 FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS  
 LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL  
 TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW  
 CA 2259830 A1 20000720 (200051) EN  
 AU 2000030289 A 20000807 (200055)  
 US 2002143164 A1 20021003 (200267)

# APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000043510	A2	WO 2000-CA42	20000120
CA 2259830	A1	CA 1999-2259830	19990120
AU 2000030289	A	AU 2000-30289	20000120
US 2002143164	A1 Cont of	WO 2000-CA42	20000120
		US 2001-911826	20010720

# FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000030289	A Based on	WO 200043510

# PRIORITY APPLN. INFO: CA 1999-2259830 19990120

AN 2000-499228 [44] WPIDS

AB WO 200043510 A UPAB: 20000913

NOVELTY - A guanine nucleotide releasing factor (GRF)-4 (Ras activator) nucleic acid molecule (I) and its corresponding protein (II) which has an important role in cell signaling, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) an isolated nucleic acid molecule (I) encoding a polypeptide having guanine nucleotide releasing factor (GRF) 4 activity;

(2) an isolated polypeptide (II) having \*\*\*GRF4\*\*\* activity and a CDC25 domain;

(3) a mimetic (II') of (II) with \*\*\*GRF4\*\*\* activity;

(4) a recombinant nucleic acid molecule comprising (I) operatively linked to a promoter that enhances transcription of (I) in a host cell;

(5) a system (III) for the expression of \*\*\*GRF4\*\*\* comprising an expression vector into which (I) is inserted;

(6) a cell transformed with (III);

(7) a method (IV) for expressing a polypeptide comprising transforming an expression host with an expression vector and culturing the expression host;

(8) a \*\*\*GRF4\*\*\* specific antibody (V) targeted to a region selected from either the C-terminus, the CDC25 domain, the CNMP binding domain and the PDZ domain;

(9) a method (VI) of treating a disorder characterized by excessive \*\*\*GRF4\*\*\* expression, concentration and/or activity, comprising administering an agent that reduces or inhibits \*\*\*GRF4\*\*\* polypeptide expression, concentration or activity;

(10) a method (VII) of treating a disorder characterized by inadequate \*\*\*GRF4\*\*\* expression, concentration and/or activity, comprising administering an agent that increases \*\*\*GRF4\*\*\* polypeptide expression, concentration or activity;

(11) a method (VIII) of identifying a compound that modulates the interaction of \*\*\*GRF4\*\*\* with Ras, comprising:

(a) contacting \*\*\*GRF4\*\*\*, a Ras-binding fragment of \*\*\*GRF4\*\*\* or a derivative of \*\*\*GRF4\*\*\* (X) with Ras, a \*\*\*GRF4\*\*\* -binding fragment of Ras or a derivative of Ras (Y) in the presence of the candidate compound ((X) and (Y) are capable of binding); and

(b) determining whether the binding between (X) and (Y) is modulated, therefore indicating whether the candidate compound modulates the interaction of \*\*\*GRF4\*\*\* and Ras;

(12) a method (IX) of identifying a compound that modulates the interaction of \*\*\*GRF4\*\*\* with Rap1, comprising:

(a) contacting \*\*\*GRF4\*\*\*, a Rap1-binding fragment of \*\*\*GRF4\*\*\* or a derivative of \*\*\*GRF4\*\*\* (X) with Rap1, a \*\*\*GRF4\*\*\* -binding fragment of Rap1 or a derivative of Rap1 (Y) in the presence of the candidate compound ((X) and (Y) are capable of binding); and

(b) determining whether the binding between (X) and (Y) is modulated, therefore indicating whether the candidate compound modulates the

interaction of \*\*\*GRF4\*\*\* and Rap1;

(13) a method (X) of evaluating the cell proliferation inducing properties of a candidate compound, comprising contacting the compound with:

(a) \*\*\*GRF4\*\*\*, a Ras binding fragment of \*\*\*GRF4\*\*\* or a derivative \*\*\*GRF4\*\*\*; and

(b) Ras, a \*\*\*GRF4\*\*\* binding fragment of Ras or a derivative of Ras (the \*\*\*GRF4\*\*\* and Ras are capable of binding); and

(c) determining the ability of the compound to interfere with the binding of the \*\*\*GRF4\*\*\* and Ras (the ability to reduce binding indicates that the compound reduces cell proliferation);

(14) a \*\*\*GRF4\*\*\* polypeptide Ras activator;

(15) a Ras binding peptide comprising 10 to 100 amino acids and includes part of (A1), (A2), (A3) and/or (A4) ((A2), (A3) and (A4) are defined sequences given in the specification) or a derivative of them that inhibits Ras activation; and

(16) a method of evaluating an anti-proliferative compound comprising contacting the candidate compound with the CDC25 domain of \*\*\*GRF4\*\*\* (or a derivative) and determining the ability of the candidate compound to bind to the \*\*\*GRF4\*\*\* (the ability to bind indicates that the compound inhibits cell proliferation).

ACTIVITY - None given.

No data given.

MECHANISM OF ACTION - \*\*\*GRF4\*\*\* activates Ras both in vitro and in vivo. It directly binds cyclic adenosine monophosphate (cAMP) directly via its cNMP-BD (cAMP/guanine monophosphate (cGMP) binding domain).

\*\*\*GRF4\*\*\* directly connects cAMP-generating (e.g. G protein coupled receptors) or cGMP-generating pathways to Ras. \*\*\*GRF4\*\*\* activates Ras in response to elevation of intracellular cAMP and/or cGMP.

\*\*\*GRF4\*\*\* is a target for Nedd4 ubiquitination as it binds Nedd4.

Activation of the Ras signaling pathway controls numerous cellular functions, such as cell metabolism, proliferation, differentiation and transformation. Therefore modulation of Ras activity may provide a mechanism for controlling diseases.

USE - (I) and the GRF4 protein (II) it encodes may be used in the treatment of diseases associated with inappropriate GRF4 expression and activity such as cancers and neuronal disorders. For example, (I) (and vectors containing (I) (i.e. (III))) and the GRF4 polypeptide may be used to treat disorders associated with decreased GRF4 expression.

(I) or (III) may be administered to treat diseases by rectifying mutations or deletions in a patient's genome that affect the activity of GRF4 by expressing inactive proteins or to supplement the patients own production of GRF4 polypeptides. Conversely, antisense nucleic acid molecules may be administered to down regulate GRF4 expression by binding with the cells own GRF4 genes and preventing their expression.

The GRF4 polypeptides may be used as antigens in the production of antibodies against GRF4 and in assays to identify modulators (agonists and antagonists) of GRF4 expression and activity. The anti-GRF4 antibodies and GRF4 antagonists may also be used to down regulate GRF4 expression and activity. Inhibition of Ras can reduce cellulose proliferation and cancers.

Dwg.0/24

L3 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2

ACCESSION NUMBER: 1995:83548 BIOSIS

DOCUMENT NUMBER: PREV199598097848

TITLE: Two differentially regulated nitrate reductases required for nitrate-dependent, microaerobic growth of *Bradyrhizobium japonicum*.

AUTHOR(S): Fernandez-Lopez, Manuel; Olivares, Jose; Bedmar, Eulogio J. (1)

CORPORATE SOURCE: (1) Dep. Microbiol., Estacion Exp. del Zaidin, CSIC E-419, E-18080 Granada Spain

SOURCE: Archives of Microbiology, (1994) vol. 162, No. 5, pp. 310-315.  
ISSN: 0302-8933.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Native PAGE of Triton X-100-solubilized membranes from *Bradyrhizobium japonicum* strain PJ17 grown microaerobically (2% O<sub>2</sub>, v/v) in defined nitrate-containing medium resolved two catalytically active nitrate reductase (NR) species with apparent molecular masses of 160 kDa (NR-I) and 200 kDa (NR-II). NR-I and NR-II were also found in membranes from cells of strain PJ17 that were first grown in defined medium with glutamate and further incubated microaerobically in the presence of 5 mmol/l KNO<sub>3</sub>. However, only NR-I was detected in cell membranes of strain PJ17 when nitrate was omitted from the microaerobic incubation medium.

Four mutants unable to grow at low O-2 tension in the presence of nitrate were isolated after transposon Tn5 mutagenesis. Membranes from mutants GRF110 and GRF116 showed mainly NR-I, while the other two mutants, GRF3 and \*\*\*GRF4\*\*\*, expressed mostly NR-II. These results indicate that the ability of *B. japonicum* P117 to grow under microaerobic conditions depends upon the presence of two membrane-bound NR enzymes whose synthesis seem to be independently induced by microaerobiosis (NR-I) or by both microaerobiosis and nitrate (NR-II).

=> d 12 ibib abs 1-2

L2 ANSWER 1 OF 2 WPIDS (C) 2003 THOMSON DERWENT  
 ACCESSION NUMBER: 2000-499228 [44] WPIDS  
 DOC. NO. NON-CPI: N2000-370021  
 DOC. NO. CPI: C2000-149852  
 TITLE: Nucleic acids encoding guanine nucleotide releasing factor-4 useful for the treatment of cancers and neuronal disorders.  
 DERWENT CLASS: B04 D16 S03  
 INVENTOR(S): PHAM, N; ROTIN, D  
 PATENT ASSIGNEE(S): (HSCR-N) HSC RES & DEV LP; (PHAM-I) PHAM N; (ROTI-I) ROTIN D  
 COUNTRY COUNT: 90  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000043510	A2	20000727	(200044)*	EN	88
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
CA 2259830	A1	20000720	(200051)	EN	
AU 2000030289	A	20000807	(200055)		
US 2002143164	A1	20021003	(200267)		

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000043510	A2	WO 2000-CA42	20000120
CA 2259830	A1	CA 1999-2259830	19990120
AU 2000030289	A	AU 2000-30289	20000120
US 2002143164	A1 Cont of	WO 2000-CA42	20000120
		US 2001-911826	20010720

#### FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000030289	A Based on	WO 200043510

PRIORITY APPLN. INFO: CA 1999-2259830 19990120

AN 2000-499228 [44] WPIDS

AB WO 200043510 A UPAB: 20000913

NOVELTY - A guanine nucleotide releasing factor (GRF)-4 ( \*\*\*Ras\*\*\* activator) nucleic acid molecule (I) and its corresponding protein (II) which has an important role in cell signaling, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

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(2) an isolated polypeptide (II) having \*\*\*GRF4\*\*\* activity and a CDC25 domain;

(3) a mimetic (II') of (II) with \*\*\*GRF4\*\*\* activity;

(4) a recombinant nucleic acid molecule comprising (I) operatively linked to a promoter that enhances transcription of (I) in a host cell;

(5) a system (III) for the expression of \*\*\*GRF4\*\*\* comprising an expression vector into which (I) is inserted;

(6) a cell transformed with (III);

(7) a method (IV) for expressing a polypeptide comprising transforming an expression host with an expression vector and culturing the expression host;

(8) a \*\*\*GRF4\*\*\* specific antibody (V) targeted to a region

selected from either the C-terminus, the CDC25 domain, the cAMP binding domain and the PDZ domain;

(9) a method (VI) of treating a disorder characterized by excessive \*\*\*GRF4\*\*\* expression, concentration and/or activity, comprising administering an agent that reduces or inhibits \*\*\*GRF4\*\*\* polypeptide expression, concentration or activity;

(10) a method (VII) of treating a disorder characterized by inadequate \*\*\*GRF4\*\*\* expression, concentration and/or activity, comprising administering an agent that increases \*\*\*GRF4\*\*\* polypeptide expression, concentration or activity;

(11) a method (VIII) of identifying a compound that modulates the interaction of \*\*\*GRF4\*\*\* with \*\*\*Ras\*\*\*, comprising:

(a) contacting \*\*\*GRF4\*\*\*, a \*\*\*Ras\*\*\*-binding fragment of \*\*\*GRF4\*\*\* or a derivative of \*\*\*GRF4\*\*\* (X) with \*\*\*Ras\*\*\*, a \*\*\*Ras\*\*\*-binding fragment of \*\*\*Ras\*\*\* or a derivative of \*\*\*Ras\*\*\* (Y) in the presence of the candidate compound ((X) and (Y) are capable of binding); and

(b) determining whether the binding between (X) and (Y) is modulated, therefore indicating whether the candidate compound modulates the interaction of \*\*\*GRF4\*\*\* and \*\*\*Ras\*\*\*;

(12) a method (IX) of identifying a compound that modulates the interaction of \*\*\*GRF4\*\*\* with \*\*\*Rap1\*\*\*, comprising:

(a) contacting \*\*\*GRF4\*\*\*, a \*\*\*Rap1\*\*\*-binding fragment of \*\*\*GRF4\*\*\* or a derivative of \*\*\*GRF4\*\*\* (X) with \*\*\*Rap1\*\*\*, a \*\*\*Rap1\*\*\*-binding fragment of \*\*\*Rap1\*\*\* or a derivative of \*\*\*Rap1\*\*\* (Y) in the presence of the candidate compound ((X) and (Y) are capable of binding); and

(b) determining whether the binding between (X) and (Y) is modulated, therefore indicating whether the candidate compound modulates the interaction of \*\*\*GRF4\*\*\* and \*\*\*Rap1\*\*\*;

(13) a method (X) of evaluating the cell proliferation reducing properties of a candidate compound, comprising contacting the compound with:

(a) \*\*\*GRF4\*\*\*, a \*\*\*Ras\*\*\* binding fragment of \*\*\*GRF4\*\*\* or a derivative of \*\*\*GRF4\*\*\*; and

(b) \*\*\*Ras\*\*\*, a \*\*\*GRF4\*\*\* binding fragment of \*\*\*Ras\*\*\* or a derivative of \*\*\*Ras\*\*\* (the \*\*\*GRF4\*\*\* and \*\*\*Ras\*\*\* are capable of binding); and

(c) determining the ability of the compound to interfere with the binding of the \*\*\*GRF4\*\*\* and \*\*\*Ras\*\*\* (the ability to reduce binding indicates that the compound reduces cell proliferation);

(14) a \*\*\*GRF4\*\*\* polypeptide \*\*\*Ras\*\*\* activator;

(15) a \*\*\*Ras\*\*\* binding peptide comprising 10 to 100 amino acids and includes part of (A1), (A2), (A3) and/or (A4) ((A2), (A3) and (A4) are defined sequences given in the specification) or a derivative of them that inhibits \*\*\*Ras\*\*\* activation; and

(16) a method of evaluating an anti-proliferative compound comprising contacting the candidate compound with the CDC25 domain of \*\*\*GRF4\*\*\* (or a derivative) and determining the ability of the candidate compound to bind to the \*\*\*GRF4\*\*\* (the ability to bind indicates that the compound inhibits cell proliferation).

ACTIVITY - None given.

No data given.

MECHANISM OF ACTION - \*\*\*GRF4\*\*\* activates \*\*\*Ras\*\*\* both in vitro and in vivo. It directly binds cyclic adenosine monophosphate (cAMP) directly via its cNMP-BD (cAMP/guanine monophosphate (cGMP) binding domain). \*\*\*GRF4\*\*\* directly connects cAMP-generating (e.g. G protein coupled receptors) or cGMP-generating pathways to \*\*\*Ras\*\*\*. \*\*\*GRF4\*\*\* activates \*\*\*Ras\*\*\* in response to elevation of intracellular cAMP and/or cGMP. \*\*\*GRF4\*\*\* is a target for Nedd4 ubiquitination as it binds Nedd4.

Activation of the \*\*\*Ras\*\*\* signaling pathway controls numerous cellular functions, such as cell metabolism, proliferation, differentiation and transformation. Therefore modulation of \*\*\*Ras\*\*\* activity may provide a mechanism for controlling diseases.

USE - (I) and the GRF4 protein (II) it encodes may be used in the treatment of diseases associated with inappropriate GRF4 expression and activity such as cancers and neuronal disorders. For example, (I) (and vectors containing (I) (i.e. (III))) and the GRF4 polypeptide may be used to treat disorders associated with decreased GRF4 expression.

(I) or (III) may be administered to treat diseases by rectifying mutations or deletions in a patient's genome that affect the activity of GRF4 by expressing inactive proteins or to supplement the patients own production of GRF4 polypeptides. Conversely, antisense nucleic acid molecules may be administered to down regulate GRF4 expression by binding with the cells own GRF4 genes and preventing their expression.

The GRF4 polypeptides may be used as antigens in the production of

antibodies against GRF4 and in assays to identify modulators (agonists and antagonists) of GRF4 expression and activity. The anti-GRF4 antibodies and GRF4 antagonists may also be used to down regulate GRF4 expression and activity. Inhibition of Ras can reduce cell proliferation and cancers.  
Dwg.0/24

L2 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:513799 CAPLUS

DOCUMENT NUMBER: 133:130799

TITLE: Protein and cDNA sequences of a novel human guanine nucleotide releasing factor 4 ( \*\*\*GRF4\*\*\* ) and the therapeutic uses thereof

INVENTOR(S): Rotin, Daniela; Pham, Nam

PATENT ASSIGNEE(S): HSC Research and Development Limited Partnership, Can.

SOURCE: PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043510	A2	20000727	WO 2000-CA42	20000120
WO 2000043510	A3	20001221		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2360770	AA	20000727	CA 2000-2360770	20000120
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US 2002143164	A1	20021003	US 2001-911826	20010720
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PRIORITY APPLN. INFO.:

CA 1999-2259830	A	19990120
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WO 2000-CA42	W	20000120
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AB The invention relates to protein and cDNA sequences of a novel human guanine nucleotide releasing factor 4 ( \*\*\*GRF4\*\*\* ) \*\*\*GRF4\*\*\* that is a \*\*\*Ras\*\*\* activator, and its corresponding protein which has an important role in cell signaling. \*\*\*GRF4\*\*\* contains several domains, including CDC25, REM, RA, PDZ and a CNMP (cAMP/cGMP) binding domain (CNMP-BD), 2 PY motifs and a C terminal SxV sequence. \*\*\*GRF4\*\*\* can activate \*\*\*Ras\*\*\* in vitro or in vitro, it binds cAMP directly via its CNMP-BD. \*\*\*GRF4\*\*\* directly connects cAMP-generating or cGMP-generating pathways to \*\*\*Ras\*\*\*. \*\*\*GRF4\*\*\* is expressed mainly in the brain, and is localized at the plasma membrane, a localization dependent on the presence of intact PDZ domain. The invention also relates to methods of using these nucleic acid sequences and proteins in medical treatments and drug screening.